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Enantioselective Synthesis of 6-Oxygenated Atisine Derivative *via* Intramolecular Double Michael Reaction

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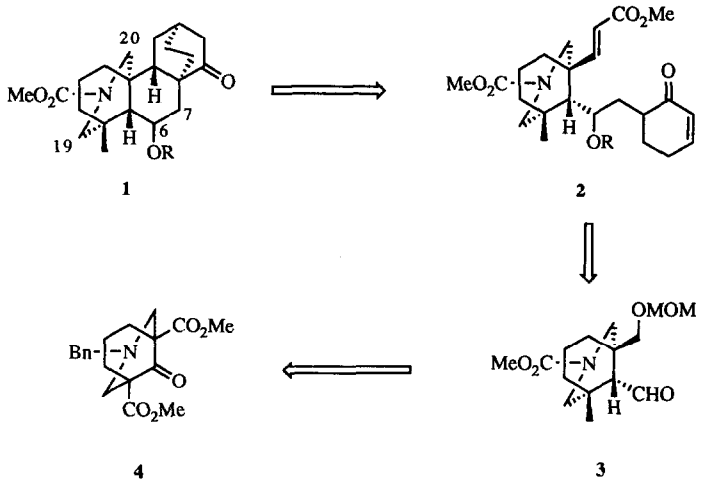
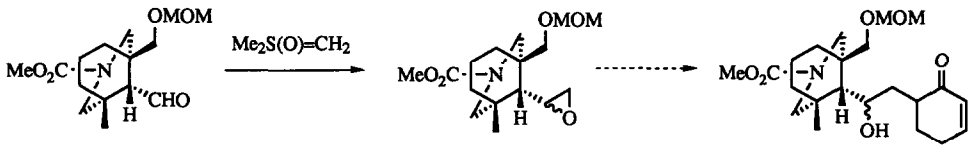
Abstract: *An enantioselective synthesis of a 6-oxygenated atisine derivative* ***20*** *is described. The atisine skeleton* ***18*** *was stereoselectively constructed by the intramolecular double Michael reaction of the enone ester* ***16****, derived, through the aldehyde* ***3****, from the symmetrical ketone* ***4****.*

The diterpenoid alkaloids have long been of interest because of their pharmacological properties, complex molecular structure, and interesting chemistry.[1] Recently, we achieved the synthesis of atisine[2] in a naturally occurring enantiomeric form *via* the intramolecular double Michael reaction as a key step.[3] The further extension of this strategy to the synthesis of other alkaloids has fascinated us. A number of diterpenoid alkaloids possess oxygen functionalities on the ring B,[1] and it is considered that the oxygen group at the C-6 position would assist in the bond formation between the C-7 and the C-20. Thus a synthesis of a 6-oxygenated atisine derivative **1** was examined as a preliminary experiment intending the total synthesis of diterpenoid alkaloids having a more complicated architecture. It was further planned that the substrate **2** of the key reaction could be prepared from the aldehyde **3**, enantioselectively derivatized from the symmetrical ketone **4** (Scheme 1).[3]



Scheme 1

It is assumed that the transformation of the aldehyde **3** into the cyclohexenone **6** would be feasibly performed *via* the epoxide **5** (Scheme 2). Thus, **3** was first treated with trimethyloxosulfonium iodide[4] in dimethyl sulfoxide (DMSO) to provide **5** in 74% yield as an inseparable mixture of two diastereoisomers. Determination of the ratio of two stereoisomers by NMR spectroscopy was difficult because of the complication due to the rotational isomers of the carbamate group. Reactions of **5** with the anion derived from cyclohexenone under various conditions gave no desired compound **6**.

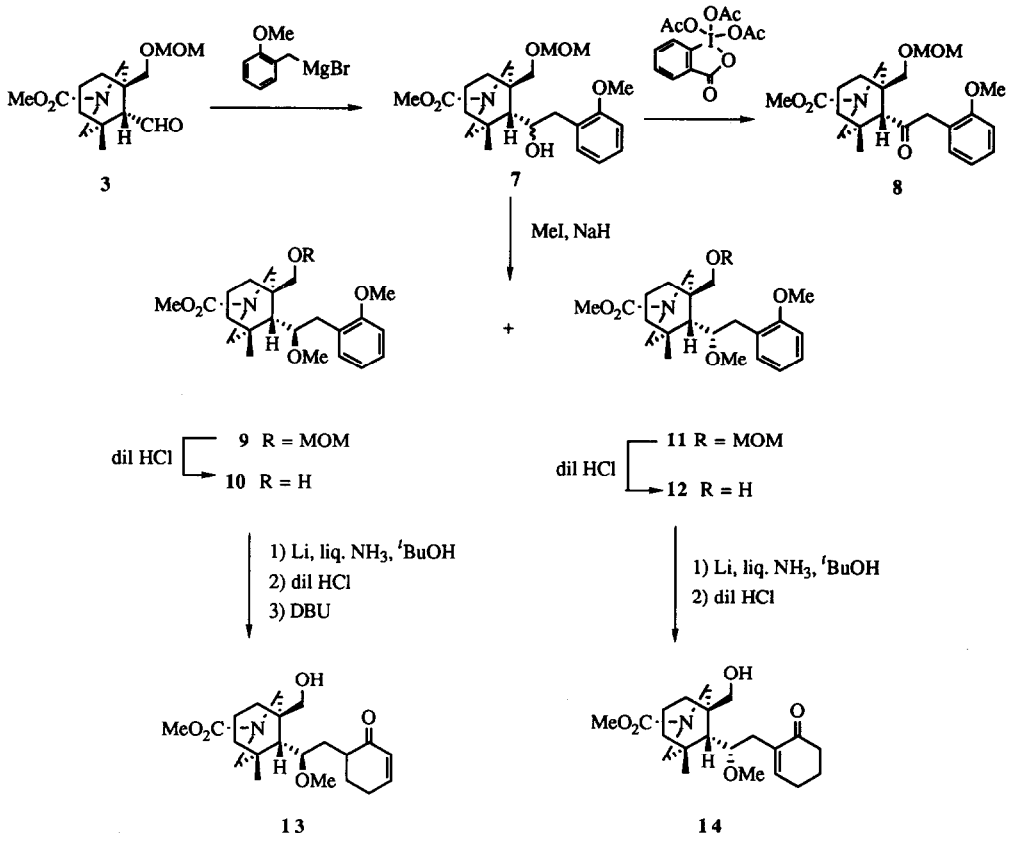


3 **5** **6**

Scheme 2

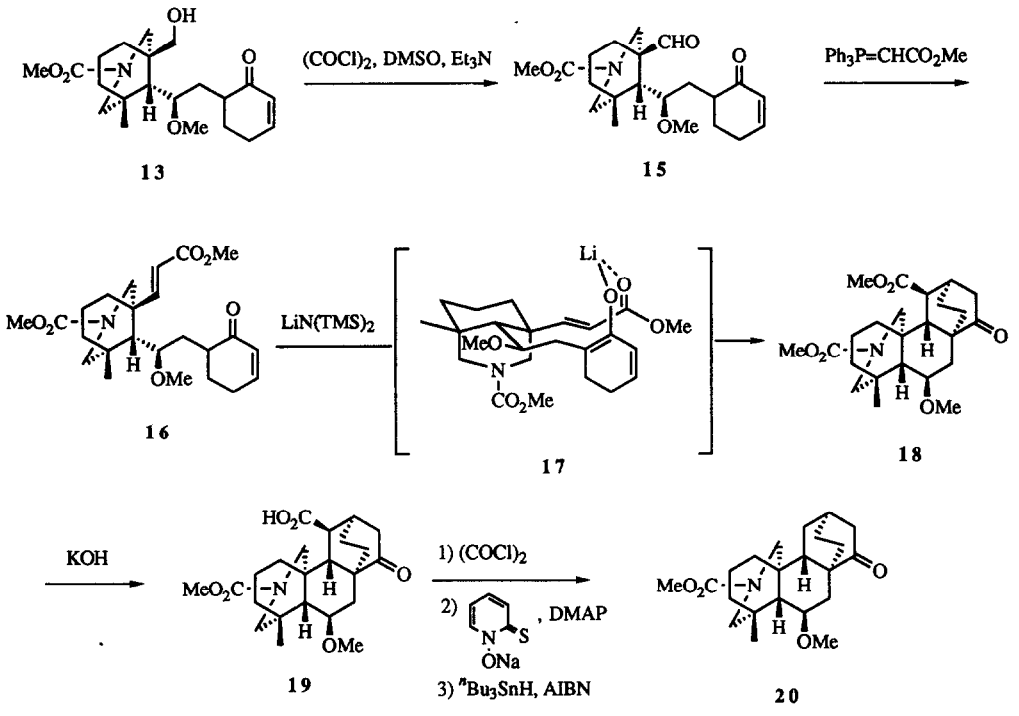
Introduction of the seven carbon unit accompanied by the oxygen function was achieved by the reaction of **3** with the benzylmagnesium bromide (Scheme 3). Inseparable 1:1 mixture of two diastereoisomers at the newly introduced stereogenic center, obtained in 97% yield, produced the single ketone **8** in 97% yield on oxidation using Dess-Martin triacetoxyperiodinane.[5] The two diastereoisomers formed were readily separated after methylation carried out in 89% yield, using methyl iodide in the presence of sodium hydride in dimethylformamide (DMF). The one stereoisomer **9** was subjected, after the removal of the methoxymethyl group with hydrochloric acid in methanol (96% yield), to Birch reduction using lithium in the presence of *tert*-butanol in liquid ammonia and tetrahydrofuran (THF). Treatment of the crude product with hydrochloric acid afforded the mixture of the α,β-unsaturated ketone **13** and the corresponding β,γ-unsaturated ketone. Further treatment of the mixture with 1,8-diazabicylo[5.4.0]undec-7-ene (DBU) in refluxing benzene provided the desired ketone **13** in 58% overall yield from **10**. On the other hand, the other stereoisomer **11** was transformed through **12** into the unexpected enone **14** in 72% overall yield by the similar procedures as above except the treatment with DBU. It is noteworthy that the course of Birch reduction was completely changed by the stereochemistry of the oxygen functionality although the reason was obscure. The configurations at the methoxy group were determined by the following transformation of **13** into the pentacyclic compound **18**.

The above enone **13** was converted into the substrate **16** of the key reaction in two steps; Swern oxidation (93% yield) followed by the Wittig reaction using the stable ylide in hot acetonitrile (99% yield) (Scheme 4). The intramolecular double Michael reaction of **16** was carried out using several bases and several solvent systems including 2,5-dimethyltetrahydrofuran. The best result was obtained by the reaction conducting with lithium hexamethyldisilazide for 45 min at -78 °C and then for 45 min at room temperature in a mixture of hexane and ether (about 6:1 v/v). The pentracyclic compound **18**, which would be formed *via* the conformation **17** chelating



Scheme 3

with lithium ion, was produced in 62% yield as a single stereoisomer. In the 500 MHz ^{1}H NMR spectrum, the hydrogens at the C-5 and the C-6 position were observed at 1.24 ppm as doublet with J = 11.3 Hz and 3.51 p.p.m. as double double doublet with J = 5.6, 8.3, and 11.3 Hz, respectively. Two hydrogens at the C-7 position were separately resonated at 1.74 ppm as double doublet with J = 8.3 and 15.0 Hz and at 1.89 ppm as double doublet with J = 5.6 and 15.0 Hz. The fact indicated the axially oriented hydrogen at the C-6 position. Hydrolysis of **18** with potassium hydroxide in hot aqueous ethanol gave, in 61% yield, the carboxylic acid **19**, whose carboxyl group was removed by the Barton's procedure.[6] Thus, after conversion of **19** into the acid chloride, its treatment with 2-mercaptopyridine-1-oxide sodium salt in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP), followed by radical reduction using tri-*n*-butyltin hydride and azoisobutyronitrile (AIBN), produced the ketone **20** in 81% overall yield from **19**. Thus enantioselective synthesis of the atisine derivative possessing the oxygen functionality at the C-6 position was achieved.



Scheme 4

Experimental

General. IR spectra were taken with Hitachi 260-10 and JASCO-IR-Report-100 spectrophotometers. ^1H NMR spectra were measured on Hitachi R-1200, JEOL FX-90A and JEOL-GX-500 spectrometers with $CDCl_3$ as solvent and are recorded in ppm relative to internal tetramethylsilane. Mass spectra were measured with JEOL-DX-300 and JEOL-JMS-DX-303 instruments. Specific optical rotations were measured on a JASCO-DIP-340 polarimeter. All reactions were run under an atmosphere of dry N_2 or Ar. Solvents were freshly distilled prior to use; THF, Et_2O, toluene, hexane and benzene were distilled from Na-benzophenone; CH_2Cl_2, DMF, DMSO, and MeCN were distilled from CaH_2 and kept over 4 Å molecular sieves. Silica gel column chromatography was carried out with Merck Kiesel gel 60 Art 7734^R and flash chromatography was performed using Merck Kiesel gel 60 Art 9387^R. HPLC was carried out with a Gilson HPLC system Model 302/303 and monitored using UV and refractive index detectors. Oily NaH and KH were washed with dry hexane three times prior to use. All new compounds described in this Experimental section were homogeneous on TLC and HPLC.

(1*R*,5*R*,9*R*)-3-Methoxycarbonyl-1-methoxymethyloxymethyl-5-methyl-9-oxiranyl-3-azabicyclo[3.3.1]nonane (5). To a stirred solution of NaH in oil (60%; 94.7 mg, 2.37 mmol) in dry DMSO (3 mL) was added slowly at room temperature a solution of trimethyloxosulfonium iodide[4] (571 mg, 2.59 mmol) in dry DMSO (3 mL). After having been stirred for 5 min at the same temperature, to the resulting mixture was added slowly a solution of the aldehyde **3**[3] (115 mg, 0.38 mmol) in dry DMSO (4 mL), and the mixture was stirred for 25 min at the same temperature and for 2 h at 50 °C. After addition of H_2O at 0 °C, the mixture was thoroughly extracted with $CHCl_3$. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel with hexane-AcOEt (4:1 v/v) as eluant to give the epoxide **5** (88.8 mg, 74%) as a colorless oil: IR (neat) 1750, 1247 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 and 0.95 [1.5 H (1:1.1), each s, 5-Me], 1.03 and 1.04 [1.5 H (1.1:1), each s, 5-Me], 3.35 and 3.36 [3 H (1:1.1), each s, CH_2OMe], 3.71 and 3.72 [3 H (1:3.2), each s, NCO_2Me], 4.58-4.65 [2 H, m, OCH_2O]; EIMS *m/z* 313 (M^+); HRMS calcd for $C_{16}H_{27}NO_5$ 313.1888, found 313.1889.

(1*R*,5*R*,9*R*)-9-[1-Hydroxy-2-(*o*-methoxyphenyl)ethyl]-3-methoxycarbonyl-1-methoxymethyloxymethyl-5-methyl-3-azabicyclo[3.3.1]nonane (7). To a mixture of Mg (153 mg, 6.36 mmol), activated by heating for 6 h at 140 °C, and a catalytic amount of I_2 in dry THF (1 mL) was added slowly at room temperature a solution of *o*-methoxybenzyl bromide (1.07 g, 5.30 mmol) in dry THF (3 mL) and the mixture was stirred for 40 min at the same temperature. To the resulting mixture was added slowly at 0 °C under stirring a solution of the aldehyde **3**[3] (395 mg, 1.32 mmol) in dry THF (9 mL). After being stirred for 10 min at 0 °C, followed by addition of saturated aqueous NH_4Cl at 0 °C, the mixture was filtered through Celite to remove the excess Mg. The filtrate was thoroughly extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel. Elution with hexane-AcOEt (3:1 v/v) afforded the inseparable mixture of two alcohols **7** (537 mg, 97%) as a colorless oil (Found: C, 64.59; H, 8.48; N, 3.20. $C_{23}H_{35}NO_6 \cdot 0.3\ H_2O$: requires C, 64.60; H; 8.26; N, 3.28): IR ($CHCl_3$) 3460, 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77 and 0.79 [1.1 H (1:1.1), each s, 5-Me], 1.20 and 1.21 [1.9 H (1.1:1), each s, 5-Me], 3.29 and 3.30 [1.4 H (1.1:1), each s, CH_2OMe], 3.40 (1.6 H, s, CH_2OMe), 3.67 and 3.68 [3 H (1.1:1), each s, NCO_2Me], 3.80 and 3.81 [3 H (1.1:1), each s, $ArOMe$], 4.57 and 4.70 [2 H (1:1.1), each s, OCH_2O], 6.83-6.90 (2 H, m, 2 x ArH), 7.08-7.11 (1 H, m, ArH), 7.17-7.22 (1 H, m, ArH); EIMS *m/z* 421 (M^+); HRMS calcd for $C_{23}H_{35}NO_6$ 421.2462, found 421.2464.

(-)-(1*R*,5*R*,9*R*)-3-Methoxycarbonyl-1-methoxymethyloxymethyl-5-methyl-9-[1-oxo-2-(*o*-methoxyphenyl)ethyl]-3-azabicyclo[3.3.1]nonane (8). To a stirred solution of Dess-Martin triacetoxyperiodinane[5] (89.0 mg, 0.21 mmol) in dry CH_2Cl_2 (2 mL) was added slowly at room temperature a solution of the alcohols **7** (50.0 mg, 0.12 mmol) in dry CH_2Cl_2 (2 mL), and the mixture was stirred for 20 min at the same temperature. After being poured into a mixture of 2M aqueous $Na_2S_2O_3$ (12 mL) and saturated aqueous $NaHCO_3$ (2 mL), the mixture was stirred for 10 min at room temperature, and then thoroughly extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated under reduced pressure to afford a residue, which was chromatographed on silica gel. Elution with hexane-AcOEt (4:1 v/v) gave the ketone **8** (48.5 mg, 97%) as a colorless oil, $[\alpha]_D^{24}$ -9.7° (*c* 0.45, $CHCl_3$): IR (neat) 1700, 1688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 and 0.89 [3 H (1:1), each s, 5-Me], 2.73 and 2.76 [1 H (1:1), each s, 9-H],

3.37 (3 H, s, OMe), 3.71 (3 H, s, CO_2Me), 3.80 (3 H, s, ArO*Me*), 4.61 and 4.62 [2 H (1:1), each s, OCH_2O], 6.87-7.28 (4 H, m, 4 x ArH); EIMS *m/z* 419 (M^+); HRMS calcd for $C_{23}H_{33}NO_6$ 419.2306, found 419.2308.

(-)-(1*R*,1'*R*,5*R*,9*R*) and (+)-(1*R*,1'*S*,5*R*,9*R*)-3-Methoxycarbonyl-1-methoxymethyloxymethyl-9-[1'-methoxy-2'-(*o*-methoxyphenyl)ethyl]-5-methyl-3-azabicyclo[3.3.1]nonanes (9) and (11). To a stirred mixture of NaH in oil (60%, 55.6 mg, 1.39 mmol) in dry DMF (2 ml) was added slowly at 0 °C a solution of the alcohols **7** (117 mg, 0.28 mmol) in dry DMF (5 mL), and the mixture was stirred for 40 min at room temperature. After being cooled at 0 °C, followed by addition of MeI (0.18 mL, 2.89 mmol), the resulting mixture was stirred for 6 h at room temperature. After addition of saturated aqueous NH_4Cl, the mixture was thoroughly extracted with a mixture of benzene-AcOEt (1:1 v/v). The combined organic layers were washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was subjected to silica gel chromatography eluating with hexane-AcOEt (9:1 v/v) to afford the methyl ether **11** (53.0 mg, 45%) as an oil, $[\alpha]_D^{24}$ +44.3° (*c* 1.21, $CHCl_3$) (Found: C, 65.40; H, 8.43; N, 3.19. $C_{24}H_{37}NO_6 \cdot H_2O$: requires C, 65.27; H, 8.43; N, 3.19): IR (neat) 1700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.48 (3 H, s, 5-Me), 3.25 and 3.26 [3 H (1:1.8), each s, OMe], 3.40 and 3.41 [3 H (1:1.8), each s, CH_2OMe], 3.69 and 3.70 [3 H (1:1.8), each s, NCO_2Me], 3.83 [3 H, s, ArO*Me*], 4.69 and 4.70 [2 H (1:1.8), each s, OCH_2O], 6.83 (1H, d, *J* = 9.0 Hz, ArH), 6.91 (1 H, t, *J* = 9.0 Hz, ArH), 7.16-7.23 (2 H, m, 2 x ArH); EIMS *m/z* 436 (M^++1); HRMS calcd for $C_{24}H_{38}NO_6$ 436.2697, found 436.2699.

Further elution with hexane-AcOEt (9:1 v/v) provided the stereoisomer **9** (52.9 mg, 44%) as a colorless oil, $[\alpha]_D^{24}$ -7.2° (*c* 0.61, $CHCl_3$) (Found: C, 65.94; H, 8.47; N, 3.20. $C_{24}H_{37}NO_6$: requires C, 66.16; H, 8.57; N, 3.22): IR (neat) 1700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 and 1.23 [3 H (1:1), each s, 5-Me], 3.21 and 3.22 [3 H (1:1), each s, OMe], 3.32 and 3.35 [3 H (1:1), each s, CH_2OMe], 3.69 and 3.72 [3 H (1:1), each s, NCO_2Me], 3.83 (3 H, s, ArO*Me*), 4.22-4.37 (2 H, m, OCH_2O), 6.84 (1 H, d, *J* = 9.0 Hz, ArH), 6.88 (1 H, t, *J* = 9.0 Hz, ArH), 7.14 (1 H, d, *J* = 9.0 Hz, ArH), 7.19 (1 H, t, J = 9.0 Hz, ArH); EIMS *m/z* 436 (M^++1); HRMS calcd for $C_{24}H_{38}NO_6$ 436.2697, found 436.2699.

(+)-(1*R*,1'*R*,5*R*,9*R*)-1-Hydroxymethyl-3-methoxycarbonyl-9-[1'-methoxy-2'-(*o*-methoxyphenyl)ethyl]-5-methyl-3-azabicyclo[3.3.1]nonane (10). To a solution of **9** (58.0 mg, 0.13 mmol) in MeOH (5 mL) was added conc. HCl (0.1 mL) and the mixture was heated for 4 h under reflux. After being cooled, followed by basification with 10% ammonia, the resulting mixture was thoroughly extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated under reduced pressure to afford a residue, which was chromatographed on silica gel. Elution with hexane-AcOEt (1:1 v/v) gave the alcohol **10** (49.8 mg, 96%) as a colorless oil, $[\alpha]_D^{24}$ +24.3° (*c* 1.08, $CHCl_3$): IR ($CHCl_3$) 3450, 1680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (3 H, s, 5-Me), 3.08 and 3.09 [3 H (1.1:1), each s, OMe], 3.71 and 3.72 [3 H (1.1:1), each s, NCO_2Me], 3.83 and 3.84 [3 H (1.1:1), each s, ArO*Me*], 6.84-6.94 (2 H, m, 2 x ArH), 7.16-7.27 (2 H, m, 2 x ArH); EIMS *m/z* 391 (M^+); HRMS calcd for $C_{22}H_{33}NO_5$ 391.2357, found 391.2367.

(1*R*,1'*S*,5*R*,9*R*)-1-Hydroxymethyl-3-methoxycarbonyl-9-[1'-methoxy-2'-(*o*-methoxyphenyl)ethyl]-5-methyl-3-azabicyclo[3.3.1]nonane (12). The stereoisomer **11** (68.0 mg, 0.16 mmol) was transformed as above into the alcohol **12** (59.5 mg, 97%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.49 and 0.51 [3 H (1:1.8), each s, 5-Me], 3.34 (3 H, s, OMe), 3.70 (3 H, s, NCO_2Me), 3.84 (3 H, s, ArO*Me*),

6.86 (1 H, d, J = 8.0 Hz, ArH), 6.91 (1 H, t, J = 8.0 Hz, ArH), 7.16 (1 H, br t, J = 8.0 Hz, ArH), 7.22 (1 H, br t, J = 8.0 Hz, ArH); EIMS *m/z* 392 (M^++1); HRMS calcd for $C_{22}H_{34}NO_5$ 392.2435, found 392.2437.

(+)-(1*R*,1'*R*,5*R*,9*R*)-1-Hydroxymethyl-3-methoxycarbonyl-9-{1'-methoxy-2'-[1"-(2"-oxo)cyclohex-3"-enyl]ethyl}-5-methyl-3-azabicyclo[3.3.1]nonane (13). To a solution of the alcohol **10** (560 mg, 1.43 mmol) and ^{t}BuOH (7 mL) in dry THF (7 mL) was added slowly liq. NH_3 (about 15 mL) by distillation, and to the resulting mixture was added at -33 °C piece by piece Li (227 mg, 32.8 mmol). After having been stirred for 1 h at the same temperature, followed by evaporation of NH_3 at room temperature, the mixture was neutralized with saturated aqueous NH_4Cl. The resulting mixture was thoroughly extracted with $CHCl_3$. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated under reduced pressure to afford a residue, which was used for the following reaction without purification.

To a solution of the above crude product in CH_2Cl_2 (5 mL) was added 3N aqueous HCl (5 mL), and the mixture was vigorously stirred for 1.5 h at 60 °C. After neutralization with saturated aqueous $NaHCO_3$ at 0 °C, the mixture was thoroughly extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue, which was dissolved in dry benzene (6 mL). After addition of DBU (0.4 mL, 2.67 mmol), the mixture was heated for 2 h under reflux. After dilution with benzene, the mixture was washed with 10% aqueous $KHSO_4$ and saturated aqueous NaCl and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue, which was chromatographed on silica gel eluating with hexane-AcOEt (7:3 v/v) to provide the enone **13** (314 mg, 58% overall yield from **10**) as a colorless oil, $[\alpha]_D^{24}$ +29.6° (*c* 0.67, $CHCl_3$) (Found: C, 66.47; H, 8.76; N, 3.61. $C_{21}H_{33}NO_5$: requires C, 66.45; H, 8.76; N, 3.69): IR ($CHCl_3$) 3460, 1695, 1670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 and 1.10 [3 H (1:2), each s, 5-Me], 3.28 and 3.40 [3 H (1:2), each s, OMe], 3.72 (3 H, s, NCO_2Me), 5.95 and 6.00 [1 H (2:1), each d, J = 10.0 Hz, COC*H*=CH], 6.95-7.00 (1 H, m, COCH=C*H*); EIMS *m/z* 379 (M^+); HRMS calcd for $C_{21}H_{33}NO_5$ 379.2357, found 379.2359.

(1*R*,1'*S*,5*R*,9*R*)-1-Hydroxymethyl-3-methoxycarbonyl-9-{1'-methoxy-2'-[1"-(6"-oxo)-cyclohex-1"-enyl]ethyl}-5-methyl-3-azabicyclo[3.3.1]nonane (14). The isomeric alcohol **12** (994 mg, 2.54 mmol) was transformed as above without the treatment with DBU into the enone **14** (670 mg, 72%) as a colorless oil: IR (neat) 3450, 1695, 1675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 and 0.77 [3 H (1:1), each s, 5-Me], 3.37 (3 H, s, OMe), 3.70 (3 H, s, NCO_2Me), 6.87-6.92 (1 H, m, olefinic H); EIMS *m/z* 379 (M^+); HRMS calcd for $C_{21}H_{33}NO_5$ 379.2357, found 379.2359.

(+)-(1*R*,1'*R*,5*R*,9*R*)-1-Formyl-3-methoxycarbonyl-9-{1'-methoxy-2'-[1"-(2"-oxo)cyclohex-3"-enyl]ethyl}-5-methyl-3-azabicyclo[3.3.1]nonane (15). To a stirred solution of $(COCl)_2$ (0.05 mL, 0.57 mmol) in dry CH_2Cl_2 (1 mL) was slowly added at -78 °C, a solution of dry DMSO (0.05 mL, 0.71 mmol) in dry CH_2Cl_2 (1 mL). After having been stirred for 10 min at -78 °C, to the stirred mixture was slowly added a solution of the alcohol **13** (97.8 mg, 0.26 mmol) in dry CH_2Cl_2 (3 mL). After having been stirred for 20 min at -78 °C, to the reaction mixture was slowly added at -78 °C Et_3N (0.15 mL, 1.08 mmol). The mixture was stirred for 10 min at the same temperature and gradually warmed to room temperature. After addition of H_2O, the resulting mixture was thoroughly extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated under reduced pressure to afford a residue, which was subjected to

chromatography on silica gel. Elution with hexane-AcOEt (7:3 v/v) provided the aldehyde **15** (90.7 mg, 93%) as a colorless oil, $[\alpha]_D^{24}$ +1.7° (*c* 1.20, $CHCl_3$): IR ($CHCl_3$) 1720, 1700, 1678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (3 H, s, 5-Me), 3.24 and 3.25 [3 H (1:1.7), each s, OMe], 3.72 (3 H, s, NCO_2Me), 5.98 (1 H, d, *J* = 10.4 Hz, COC*H*=CH), 6.91 (1 H, dd, *J* = 6.1 and 10.4 Hz, COCH=C*H*), 9.35 and 9.37 [1 H (1.7:1), each s, CHO); EIMS *m/z* 377 (M^+); HRMS calcd for $C_{21}H_{31}NO_5$ 377.2200, found 377.2202.

(-)-(1*R*,1'*R*,5*R*,9*R*)-3-Methoxycarbonyl-1-(2-methoxycarbonylethenyl)-9-{1'-methoxy-2'-[1"-(2"-oxo)cyclohex-3"-enyl]ethyl}-5-methyl-3-azabicyclo[3.3.1]nonane (16). A mixture of the aldehyde **15** (126 mg, 0.33 mmol) and (methoxycarbonylmethylene)triphenylphosphorane (1.11 g, 3.33 mmol) in dry MeCN (15 mL) was heated for 3 days under reflux. Evaporation of the solvent under reduced pressure gave a residue, which was purified by chromatography on silica gel. Elution with hexane-AcOEt (7:3 v/v) provided the enone ester **16** (144 mg, 99%) as a colorless oil, $[\alpha]_D^{25}$ -42.4° (*c* 0.97, $CHCl_3$): IR (neat) 1695, 1673 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (3 H, s, 5-Me), 3.19 (3 H, s, OMe), 3.72 (3 H, s, NCO_2Me), 3.76 (3 H, s, CO_2Me), 5.74 and 5.82 [1 H (1.3:1), each d, *J* = 17.0 Hz, CH=C*H*CO_2Me], 6.01 (1 H, d, *J* = 10.0 Hz, COC*H*=CH), 6.80 (1 H, m, COCH=C*H*), 6.92 and 6.97 [1 H (1:1.3), each d, *J* = 17. 0 Hz, C*H*=CHCO_2Me]; EIMS *m/z* 433 (M^+); HRMS calcd for $C_{24}H_{35}NO_6$ 433.2462, found 433.2464.

(-)-8α,12α-Ethano-16,17-imino-6β-methoxy-*N*,11β-bis(methoxycarbonyl)-14-oxo-5β,9β,10α-podocarpane (18). To a stirred solution of 1.56 M ^{n}BuLi in hexane (0.21 mL, 0.33 mmol) in dry hexane (4.8 mL) was added at 0 °C $HN(TMS)_2$ (0.08 mL, 0.38 mmol), and the mixture was stirred for 15 min at 0 °C and then for 30 min at room temperature. After having been cooled at -78 °C, to the stirred mixture was slowly added a solution of the enone ester **16** (49.8 mg, 0.11 mmol) in dry Et_2O (0.8 mL). After having been stirred for 45 min at -78 °C, the mixture was stirred for 45 min at room temperature, and then poured onto silica gel (about 5 g) at 0 °C. Elution using AcOEt, followed by evaporation of the eluate under reduced pressure, gave a residue, which was subjected to chromatography on silica gel. Elution with hexane-AcOEt (3:2 v/v) provided the ketone **18** (30.9 mg, 62%) as a colorless oil, $[\alpha]_D^{23}$ -15.5° (*c* 1.26, $CHCl_3$): IR (neat) 1732, 1698, 1693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (3 H, s, 4-Me), 1.24 (1 H, d, *J* = 11.3 Hz, 5-H), 1.74 (1 H, dd, *J* = 8.3 and 15.0 Hz, 7β-H), 1.89 (1 H, dd, *J* = 5.6 and 15.0 Hz, 7α-H), 3.27 (3 H, s, OMe), 3.51 (1 H, ddd, *J* = 5.6, 8.3, and 11.3 Hz, 6-H), 3.68 (3 H, s, CO_2Me), 3.72 (3 H, s, NCO_2Me); EIMS *m/z* 433 (M^+); HRMS calcd for $C_{24}H_{35}NO_6$ 433.2462, found 433.2473.

(-)-8α,12α-Ethano-16,17-imino-6β-methoxy-*N*-methoxycarbonyl-14-oxo-5β,9β,10α-podocarpane-11β-carboxylic Acid (19). A mixture of the keto ester **18** (21.5 mg, 0.047 mmol) and KOH (170 mg, 3.15 mmol) in EtOH (3 mL) was heated for 3 h under reflux. Concentration of the mixture under reduced pressure gave a residue, which was acidified at 0 °C with 3 N aqueous HCl. The resulting mixture was thoroughly extracted with $CHCl_3$. The extract was washed with saturated aqueous NaCl, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel with MeOH-$CHCl_3$ (1:9 v/v) as eluant to afford the acid **19** (12.0 mg, 61%) as a pale yellowish syrup, $[\alpha]_D^{20}$ -17.4° (*c* 0.76, $CHCl_3$): IR ($CHCl_3$) 3630-3600, 1725, 1685 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.03 (3 H, s, 4-Me), 3.27 (3 H, s, OMe), 3.75 (3 H, s, NCO_2Me), 7.24-7.83 (1 H, br s, CO_2H); EIMS *m/z* 419 (M^+); HRMS calcd for $C_{23}H_{33}NO_6$ 419.2306, found 419.2308.

(-)-8α,12α-Ethano-16,17-imino-6β-methoxy-*N*-methoxycarbonyl-14-oxo-5β,9β,10α-podocarpane (20). To a solution of the carboxylic acid **19** (14.9 mg, 0.036 mmol) in dry benzene (2 mL) was added $(COCl)_2$ (0.05 mL, 0.57 mmol), and the mixture was stirred for 6 h at room temperature. Evaporation of the excess reagent and the solvent under reduced pressure and protection from moisture gave a residue, which was taken up into dry benzene (1.5 mL). Evaporation of the solvent under the same conditions as above afforded the crude acid chloride, which was used for the next reaction without purification.

A mixture of 2-mercaptopyridine-1-oxide sodium salt (30.3 mg, 0.24 mmol) and DMAP (11.0 mg, 0.09 mmol) in dry toluene (10 mL) was heated under reflux in a Dean-Stark apparatus to remove H_2O. To the resulting mixture was added a solution of the above acid chloride in dry toluene (2 mL), and the mixture was heated for 4 h under reflux. To the resulting mixture was added during 15 min a solution of $^nBu_3SnH$ (0.1 mL, 0.37 mmol) and AIBN (9.1 mg, 0.055 mmol) in dry toluene (2 mL), and the mixture was heated for 2 days under reflux. After addition of CCl_4 (3 mL) at 80 °C, the mixture was stirred for 1.5 h at the same temperature. Evaporation of the solvent under reduced pressure gave a residue, which was treated for 3 days at room temperature with a mixture of saturated aqueous KF (2 mL) and saturated I_2 in CH_2Cl_2 (2 mL). After filtration through Celite using $CHCl_3$, the filtrate was washed with 2 M aqueous $Na_2S_2O_3$ and saturated aqueous NaCl, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by silica gel chromatography with hexane-AcOEt (4:1 v/v) as eluant to provide the carbamate **20** (10.7 mg, 81%) as a colorless oil, $[\alpha]_D^{20}$ -20.1° (*c* 0.6, $CHCl_3$): IR (neat) 1725, 1700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (3 H, s, 4-Me), 1.13 (1 H, d, *J* = 10.8 Hz, 5-H), 1.71 (1 H, dd, *J* = 10.8 and 13.5 Hz, 7β-H), 1.85 (1 H, dd, *J* = 4.5 and 13.5 Hz, 7α-H). 3.27 (3 H, s, OMe), 3.49 (1 H, ddd, *J* = 4.5, 10.8 and 10.8 Hz, 6-H), 3.73 (3 H, s, NCO_2Me); EIMS *m/z* 375 (M^+); HRMS calcd for $C_{22}H_{33}NO_4$ 375.2408, found 375.2410.

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